NDA 20-685/S-043

OCT 2 3 2000

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4,BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Please refer to your supplemental new drug application dated December 22, 1999, received December 23, 1999, submitted under section *505(b)* of the Federal Food, Drug, and Cosmetic Act for Crixivan (indinavir sulfate) 100,200,333, and 400mg capsules.

We acknowledge receipt of your submissions dated:

January 24,2000	May 3,2000	September 7,2000
January 31,2000	May 4, 2000	September 22,2000
March 10,2000	August 10, 2000	September 28,2000
March 31,2000	August 25, 2000	October 10,2000
April 14, 2000	August 28,2000	October 19,2000
April 26, 2000	August 31, 2000	October 23,2000

This supplemental new drug application provides for pediatric safety data in the CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS sections of the label.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on October 23, 2000.

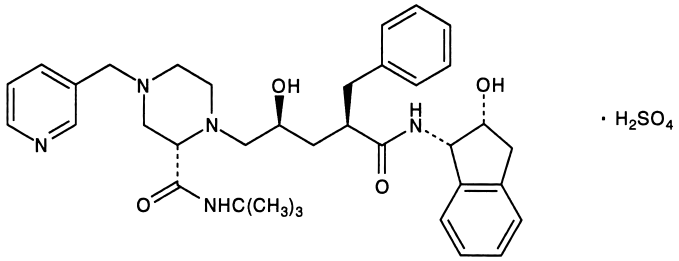
Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-685/S-043.” In addition, please provide a clean text MS Word version of the label as a desk copy. Approval of this submission by FDA is not required before the labeling is used.

CRIXIVAN®
(INDINAVIR SULFATE)
CAPSULES

DESCRIPTION

CRIXIVAN* (indinavir sulfate) is an inhibitor of the human immunodeficiency virus (HIV) protease. CRIXIVAN Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide and sodium lauryl sulfate.

The chemical name for indinavir sulfate is [1(1*S,2R*),5(*S*)]-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-(3-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl)-D-*erythro*-pentonamide sulfate (1:1) salt. Indinavir sulfate has the following structural formula:



Indinavir sulfate is a white to off-white, hygroscopic, crystalline powder with the molecular formula $C_{36}H_{47}N_5O_4 \bullet H_2SO_4$ and a molecular weight of 711.88. It is very soluble in water and in methanol.

MICROBIOLOGY

Mechanism of Action: HIV protease is an enzyme required for the proteolytic cleavage of the viral polyprotein precursors into the individual functional proteins found in infectious HIV. Indinavir binds to the protease active site and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral polyproteins resulting in the formation of immature non-infectious viral particles.

Antiretroviral Activity In Vitro: The relationship between *in vitro* susceptibility of HIV to indinavir and inhibition of HIV replication in humans has not been established. The *in vitro* activity of indinavir was assessed in cell lines of lymphoblastic and monocytic origin and in peripheral blood lymphocytes. HIV variants used to infect the different cell types include laboratory-adapted variants, primary clinical isolates and clinical isolates resistant to nucleoside analogue and nonnucleoside inhibitors of the HIV reverse transcriptase. The IC_{95} (95% inhibitory concentration) of indinavir in these test systems was in the range of 25 to 100 nM. In drug combination studies with the nucleoside analogues zidovudine and didanosine, as well as with an investigational nonnucleoside (L-697,661), indinavir showed synergistic activity in cell culture.

Drug Resistance: Isolates of HIV with reduced susceptibility to the drug have been recovered from some patients treated with indinavir. Viral resistance was correlated with the accumulation of mutations that resulted in the expression of amino acid substitutions in the viral protease. Eleven amino acid residue positions, at which substitutions are associated with resistance, have been identified. Resistance was mediated by the co-expression of multiple and variable substitutions at these positions. In general, higher levels of resistance were associated with the co-expression of greater numbers of substitutions.

Cross-Resistance to Other Antiviral Agents: Cross-resistance was noted between indinavir and the protease inhibitor ritonavir. Varying degrees of cross-resistance have been observed between indinavir and other HIV-protease inhibitors.

* Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Indinavir was rapidly absorbed in the fasted state with a time to peak plasma concentration (T_{max}) of 0.8 ± 0.3 hours (mean ± S.D.) (n=11). A greater than dose-proportional increase in indinavir plasma concentrations was observed over the 200-1000 mg dose range. At a dosing regimen of 800 mg every 8 hours, steady-state area under the plasma concentration time curve (AUC) was 30,691 ± 11,407 nM•hour (n=16), peak plasma concentration (C_{max}) was 12,617 ± 4037 nM (n=16), and plasma concentration eight hours post dose (trough) was 251 ± 178 nM (n=16).

Effect of Food on Oral Absorption: Administration of indinavir with a meal high in calories, fat, and protein (784 kcal, 48.6 g fat, 31.3 g protein) resulted in a 77% ± 8% reduction in AUC and an 84% ± 7% reduction in C_{max} (n=10). Administration with lighter meals (e.g., a meal of dry toast with jelly, apple juice, and coffee with skim milk and sugar or a meal of corn flakes, skim milk and sugar) resulted in little or no change in AUC, C_{max} or trough concentration.

Distribution: Indinavir was approximately 60% bound to human plasma proteins over a concentration range of 81 nM to 16,300 nM.

Metabolism: Following a 400-mg dose of ^{14}C-indinavir, 83 ± 1% (n=4) and 19 ± 3% (n=6) of the total radioactivity was recovered in feces and urine, respectively; radioactivity due to parent drug in feces and urine was 19.1% and 9.4%, respectively. Seven metabolites have been identified, one glucuronide conjugate and six oxidative metabolites. *In vitro* studies indicate that cytochrome P-450 3A4 (CYP3A4) is the major enzyme responsible for formation of the oxidative metabolites.

Elimination: Less than 20% of indinavir is excreted unchanged in the urine. Mean urinary excretion of unchanged drug was 10.4 ± 4.9% (n=10) and 12.0 ± 4.9% (n=10) following a single 700-mg and 1000-mg dose, respectively. Indinavir was rapidly eliminated with a half-life of 1.8 ± 0.4 hours (n=10). Significant accumulation was not observed after multiple dosing at 800 mg every 8 hours.

Special Populations

Hepatic Insufficiency: Patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of indinavir resulting in approximately 60% higher mean AUC following a single 400-mg dose (n=12). The half-life of indinavir increased to 2.8 ± 0.5 hours. Indinavir pharmacokinetics have not been studied in patients with severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION, *Hepatic Insufficiency*).

Renal Insufficiency: The pharmacokinetics of indinavir have not been studied in patients with renal insufficiency.

Gender: The effect of gender on the pharmacokinetics of indinavir was evaluated in 10 HIV seropositive women who received CRIXIVAN 800 mg every 8 hours with zidovudine 200 mg every 8 hours and lamivudine 150 mg twice a day for one week. Indinavir pharmacokinetic parameters in these women were compared to those in HIV seropositive men (pooled historical control data). Differences in indinavir exposure, peak concentrations, and trough concentrations between males and females are shown in Table 1 below:

Table 1

PK Parameter	% change in PK parameter for females relative to males	90% Confidence Interval
$AUC_{0\text{-}8h}$ (nM•hr)	↓13%	(↓32%, ↑12%)
C_{max} (nM)	↓13%	(↓32%, ↑10%)
C_{8h} (nM)	↓22%	(↓47%, ↑15%)

↓Indicates a decrease in the PK parameter; ↑indicates an increase in the PK parameter.

The clinical significance of these gender differences in the pharmacokinetics of indinavir is not known.

Race: Pharmacokinetics of indinavir appear to be comparable in Caucasians and Blacks based on pharmacokinetic studies including 42 Caucasians (26 HIV-positive) and 16 Blacks (4 HIV-positive).

Pediatric: The optimal dosing regimen for use of indinavir in pediatric patients has not been established. In HIV-infected pediatric patients (age 4-15 years), a dosage regimen of indinavir capsules, 500 mg/m^2 every 8 hours, produced $AUC_{0\text{-}8hr}$ of 38,742 ± 24,098 nM•hour (n=34), C_{max} of 17,181 ± 9809 nM (n=34), and trough concentrations of 134 ± 91 nM (n=28). The pharmacokinetic profiles of indinavir in pediatric patients were not comparable to profiles previously observed in HIV-infected adults

receiving the recommended dose of 800 mg every 8 hours. The AUC and C_{max} values were slightly higher and the trough concentrations were considerably lower in pediatric patients. Approximately 50% of the pediatric patients had trough values below 100 nM; whereas, approximately 10% of adult patients had trough levels below 100 nM. The relationship between specific trough values and inhibition of HIV replication has not been established.

Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

Specific drug interaction studies were performed with indinavir and a number of drugs.

Drugs That Should Not Be Coadministered With CRIXIVAN

Administration of indinavir (800 mg every 8 hours) with rifampin (600 mg once daily) for one week resulted in an 89% ± 9% decrease in indinavir AUC.

In a published study, eight HIV-negative volunteers received indinavir 800 mg every eight hours for four doses prior to and at the end of a 14-day course of St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) 300 mg three times daily. Indinavir plasma pharmacokinetics were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC_{0-8h} of indinavir was decreased 57% ± 19% and the C_{8h} of indinavir was decreased 81% ± 16% compared to when indinavir was taken alone. All subjects demonstrated a decrease in AUC $_{0-8h}$ (range 36 to 79%) and a decrease in C_{8h} (range 49 to 99%). (See **WARNINGS**.)

Drugs Requiring Dose Modification

Delavirdine: Preliminary data (n=14) indicate that delavirdine inhibits the metabolism of indinavir such that coadministration of a 400-mg single dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values slightly less than those observed following administration of an 800-mg dose of indinavir alone. Also, coadministration of a 600-mg dose of indinavir with delavirdine (400 mg three times a day) resulted in indinavir AUC values approximately 40% greater than those observed following administration of an 800-mg dose of indinavir alone. Indinavir had no effect on delavirdine pharmacokinetics (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Delavirdine*).

Efavirenz: When indinavir (800 mg every 8 hours) was given with efavirenz (200 mg once daily) for two weeks, the indinavir AUC and C_{max} were decreased by approximately 31% and 16%, respectively, as a result of enzyme induction. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Efavirenz.*)

Itraconazole: In a multiple-dose study, administration in the fasted state of itraconazole capsules 200 mg twice daily with indinavir 600 mg every 8 hours resulted in an indinavir AUC similar to that observed during administration of indinavir 800 mg every 8 hours alone for one week (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Itraconazole*).

Ketoconazole: In a single-dose study, administration of a 400-mg dose of ketoconazole with a 400-mg dose of indinavir resulted in a 68% ± 48% increase in indinavir AUC compared to a 400-mg dose of indinavir alone. In a multiple-dose study, administration of ketoconazole 400 mg once daily with indinavir 600 mg every 8 hours resulted in an 18% ± 17% decrease in indinavir AUC compared to an 800-mg dose of indinavir alone every 8 hours (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Ketoconazole*).

Rifabutin: The coadministration of indinavir 800 mg every 8 hours with rifabutin either 300 mg once daily or 150 mg once daily was evaluated in two separate clinical studies. The results of these studies showed a decrease in indinavir AUC (32% ± 19% and 31% ± 15%, respectively) vs. indinavir 800 mg every 8 hours alone and an increase in rifabutin AUC (204% ± 142% and 60% ± 47%, respectively) vs. rifabutin 300 mg once daily alone. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Rifabutin*.)

Drugs Not Requiring Dose Modification

Cimetidine, Quinidine, Grapefruit Juice: Administration of a single 400-mg dose of indinavir following six days of cimetidine (600 mg every 12 hours) did not affect indinavir AUC. Administration of a single 400-mg dose of indinavir with 8 oz. of grapefruit juice resulted in a decrease in indinavir AUC (26% ± 18%). Administration of a single 400-mg dose of indinavir with 200 mg of quinidine sulfate resulted in a 10% ± 26% increase in indinavir AUC.

Methadone: Administration of indinavir (800 mg every 8 hours) with methadone (20 mg to 60 mg daily) for one week resulted in no change in methadone AUC and little or no change in indinavir AUC.

Nucleoside analogue antiretroviral agents: Administration of indinavir (1000 mg every 8 hours) with zidovudine (200 mg every 8 hours) for one week resulted in a 13% ± 48% increase in indinavir AUC and a 17% ± 23% increase in zidovudine AUC. In another study, administration of indinavir (800 mg every 8

hours) with zidovudine (200 mg every 8 hours) in combination with lamivudine (150 mg twice daily) for one week resulted in no change in indinavir AUC, a 36% increase in zidovudine AUC, and a 6% decrease in lamivudine AUC. Administration of indinavir (800 mg every 8 hours) in combination with stavudine (40 mg every 12 hours) for one week resulted in no change in indinavir AUC and a 25% ± 26% increase in stavudine AUC.

*ORTHO-NOVUM 1/35:*** Administration of indinavir (800 mg every 8 hours) with ORTHO-NOVUM 1/35 for one week resulted in a 24% ± 17% increase in ethinyl estradiol AUC and a 26% ± 14% increase in norethindrone AUC.

Trimethoprim/Sulfamethoxazole, Fluconazole, Isoniazid, Clarithromycin: Administration of indinavir (400 mg every 6 hours) with trimethoprim/sulfamethoxazole (one double strength tablet every 12 hours) for one week resulted in no change in indinavir AUC, a 19% ± 31% increase in trimethoprim AUC, and no change in sulfamethoxazole AUC. Administration of indinavir (1000 mg every 8 hours) with fluconazole (400 mg once daily) for one week resulted in a 19% ± 33% decrease in indinavir AUC and no change in fluconazole AUC. Administration of indinavir (800 mg every 8 hours) with isoniazid (300 mg once daily) for one week resulted in no change in indinavir AUC and a 13% ± 15% increase in isoniazid AUC. Administration of indinavir (800 mg every 8 hours) with clarithromycin (500 mg every 12 hours) for one week resulted in a 29% ± 42% increase in indinavir AUC and a 53% ± 36% increase in clarithromycin AUC.

INDICATIONS AND USAGE

CRIXIVAN in combination with antiretroviral agents is indicated for the treatment of HIV infection.

This indication is based on two clinical trials of approximately 1 year duration that demonstrated: 1) a reduction in the risk of AIDS defining illnesses or death; 2) a prolonged suppression of HIV RNA.

Description of Studies

In all clinical studies, with the exception of ACTG 320, the AMPLICOR HIV MONITOR assay was used to determine the level of circulating HIV RNA in serum. This is an experimental use of the assay. HIV RNA results should not be directly compared to results from other trials using different HIV RNA assays or using other sample sources.

Study ACTG 320 was a multicenter, randomized, double-blind clinical endpoint trial to compare the effect of CRIXIVAN in combination with zidovudine and lamivudine with that of zidovudine plus lamivudine on the progression to an AIDS-defining illness (ADI) or death. Patients were protease inhibitor and lamivudine naive and zidovudine experienced, with CD4 cell counts of ≤200 cells/mm^3. The study enrolled 1156 HIV-infected patients (17% female, 28% Black, 18% Hispanic, mean age 39 years). The mean baseline CD4 cell count was 87 cells/mm^3. The mean baseline HIV RNA was 4.95 $\log_{10}$ copies/mL (89,035 copies/mL). The study was terminated after a planned interim analysis, resulting in a median follow-up of 38 weeks and a maximum follow-up of 52 weeks. Results are shown in Table 2 and Figures 1 & 2.

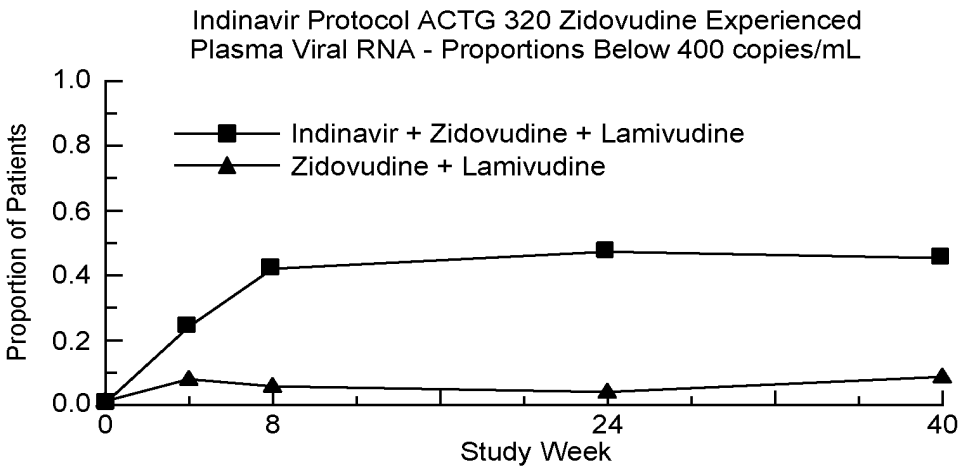
Table 2
ACTG 320

Endpoint	Number (%) of Patients with AIDS-defining Illness or Death IDV+ZDV+L (n=577)	 ZDV+L (n=579)
HIV Progression or Death	35 (6.1)	63 (10.9)
Death*	10 (1.7)	19 (3.3)

* The number of deaths is inadequate to assess the impact of Indinavir on survival.
IDV = Indinavir, ZDV = Zidovudine, L = Lamivudine

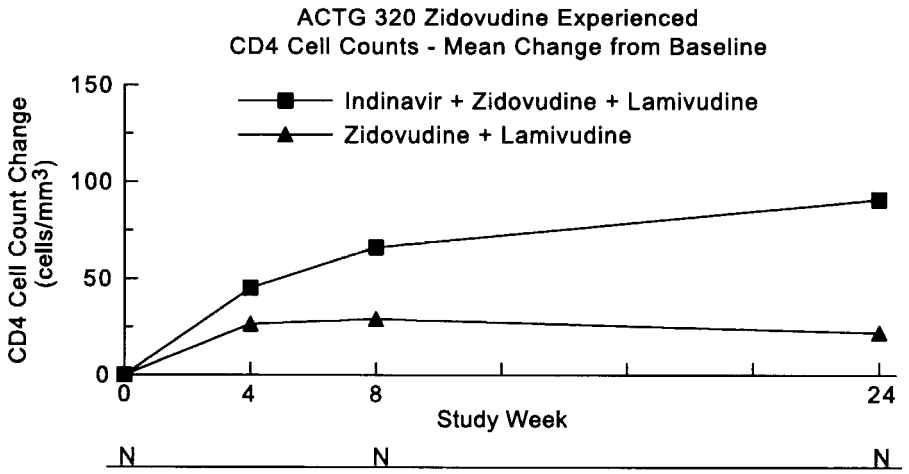
** Registered trademark of Ortho Pharmaceutical Corporation

Study ACTG 320: Figure 1



	N	N	N
IDV+ZDV+L	566	437	218
ZDV+L	573	450	231

Study ACTG 320: Figure 2



	N	N	N
IDV + ZDV + L	577	522	417
ZDV + L	579	512	423

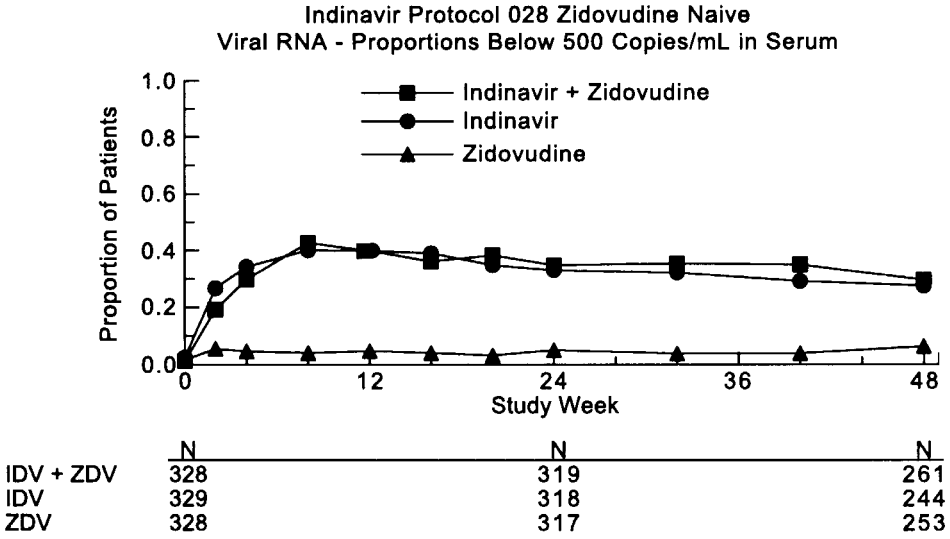
Study 028, a double-blind, multicenter, randomized, clinical endpoint trial conducted in Brazil, compared the effects of CRIXIVAN plus zidovudine with those of CRIXIVAN alone or zidovudine alone on the progression to an ADI or death, and on surrogate marker responses. All patients were antiretroviral naive with CD4 cell counts of 50 to 250 cells/mm^3. The study enrolled 996 HIV-1 seropositive patients [28% female, 11% Black, 1% Asian/Other, median age 33 years, mean baseline CD4 cell count of 152 cells/mm^3, mean serum viral RNA of 4.44 $\log_{10}$ copies/mL (27,824 copies/mL)]. Treatment regimens containing zidovudine were modified in a blinded manner with the optional addition of lamivudine (median time: week 40). The median length of follow-up was 56 weeks with a maximum of 97 weeks. The study was terminated after a planned interim analysis, resulting in a median follow-up of 56 weeks and a maximum follow-up of 97 weeks. Results are shown in Table 3 and Figures 3 and 4.

Table 3
Protocol 028

Endpoint	Number (%) of Patients with AIDS-defining Illness or Death		
	IDV+ZDV (n=332)	IDV (n=332)	ZDV (n=332)
HIV Progression or Death	21 (6.3)	27 (8.1)	62 (18.7)
Death*	8 (2.4)	5 (1.5)	11 (3.3)

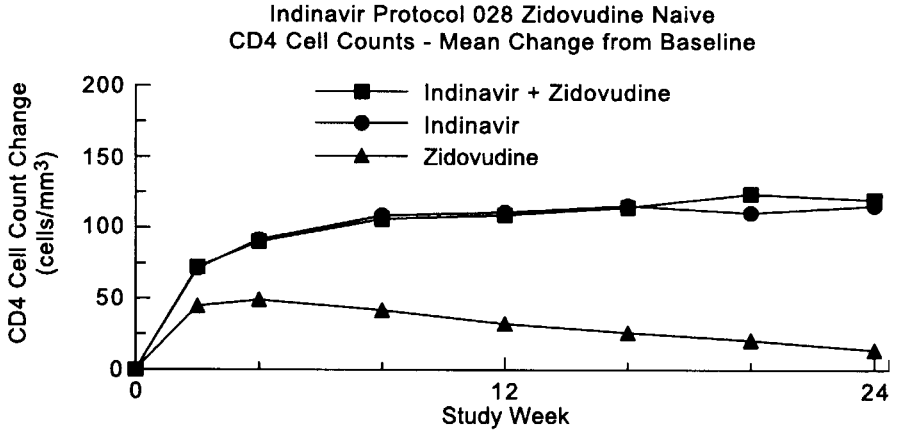
* The number of deaths is inadequate to assess the impact of Indinavir on survival.

Study 028: Figure 3



	N	N	N
IDV + ZDV	328	319	261
IDV	329	318	244
ZDV	328	317	253

Study 028: Figure 4

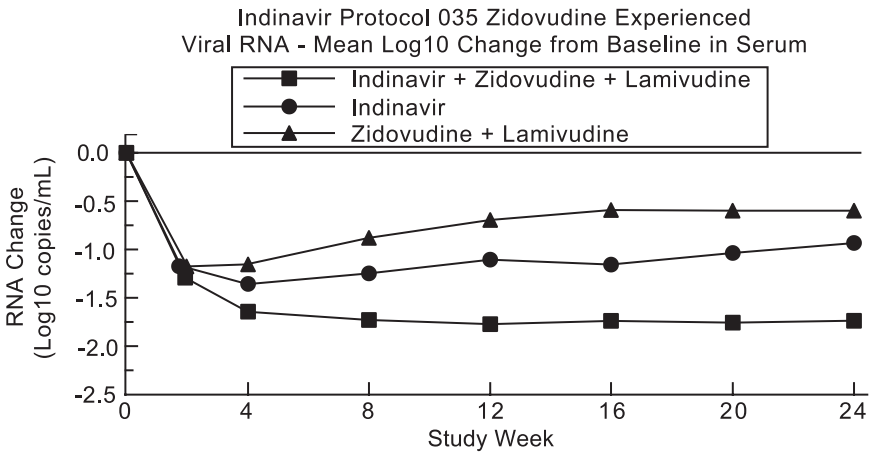


	N	N
IDV + ZDV	332	277
IDV	332	298
ZDV	332	295

Study 035 was a multicenter randomized trial in 97 HIV-1 seropositive patients who were zidovudine-experienced (median exposure 30 months), protease-inhibitor- and lamivudine-naive, with mean baseline CD4 count 175 cells/mm^3 and mean baseline serum viral RNA 4.62 $\log_{10}$ copies/mL (41,230 copies/mL).

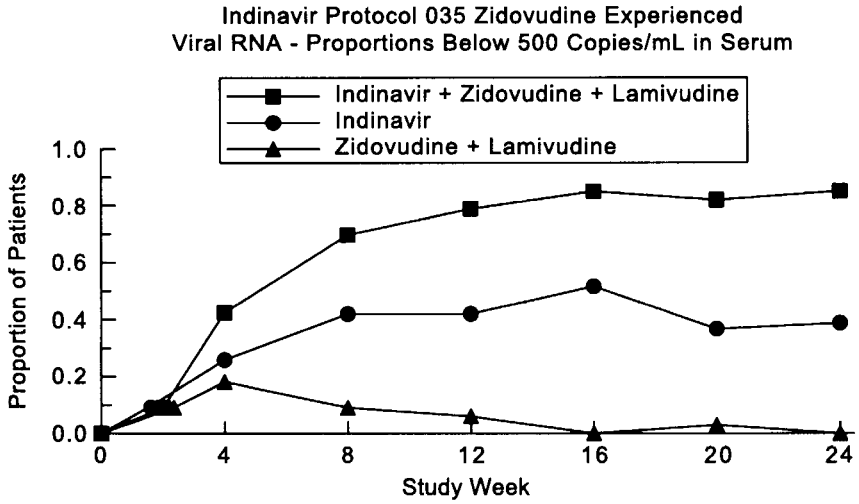
Comparisons included CRIXIVAN plus zidovudine plus lamivudine vs. CRIXIVAN alone vs. zidovudine plus lamivudine. After at least 24 weeks of randomized, double-blind therapy, patients were switched to open-label CRIXIVAN plus lamivudine plus zidovudine. Mean changes in $\log_{10}$ viral RNA in serum, the proportions of patients with viral RNA below 500 copies/mL in serum, and mean changes in CD4 cell counts, during 24 weeks of randomized, double-blinded therapy are summarized in Figures 5, 6, and 7, respectively. A limited number of patients remained on randomized, double-blind treatment for longer periods; based on this extended treatment experience, it appears that a greater number of subjects randomized to CRIXIVAN plus zidovudine plus lamivudine demonstrated HIV RNA levels below 500 copies/mL during one year of therapy as compared to those in other treatment groups.

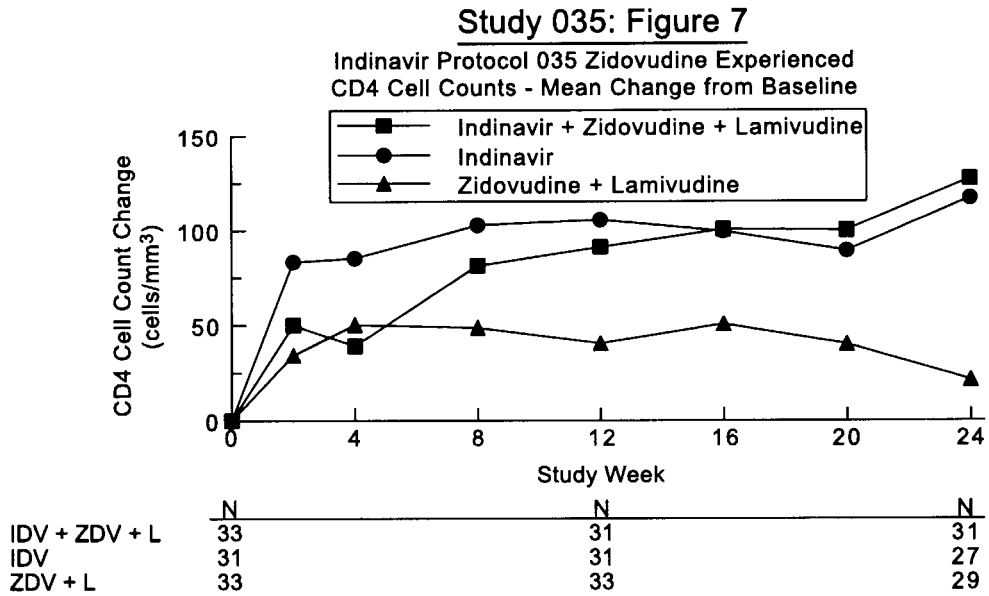
Study 035: Figure 5



	N	N	N
IDV + ZDV + L	32	30	30
IDV	31	31	28
ZDV + L	33	33	30

Study 035: Figure 6





Genotypic Resistance in Clinical Studies

Study 006 (10/15/93-10/12/94) was a dose-ranging study in which patients were initially treated with CRIXIVAN at a dose of <2.4 g/day followed by 2.4 g/day. Study 019 (6/23/94-4/10/95) was a randomized comparison of CRIXIVAN 600 mg every 6 hours, CRIXIVAN plus zidovudine, and zidovudine alone. Table 4 shows the incidence of genotypic resistance at 24 weeks in these studies.

Table 4
Genotypic Resistance at 24 Weeks

Treatment Group	Resistance to IDV n/N*	Resistance to ZDV n/N*
IDV	—	—
<2.4 g/day	31/37 (84%)	—
2.4 g/day	9/21 (43%)	1/17 (6%)
IDV/ZDV	4/22 (18%)	1/22 (5%)
ZDV	1/18 (6%)	11/17 (65%)

* N - includes patients with non-amplifiable virus at 24 weeks who had amplifiable virus at week 0.

CONTRAINDICATIONS

CRIXIVAN is contraindicated in patients with clinically significant hypersensitivity to any of its components.

CRIXIVAN should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam, pimozide, or ergot derivatives. Inhibition of CYP3A4 by CRIXIVAN could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions.

WARNINGS

Nephrolithiasis/Urolithiasis

Nephrolithiasis/urolithiasis has occurred with CRIXIVAN therapy. The frequency of nephrolithiasis is substantially higher in pediatric patients (29%) than in adult patients (9.3%). In some cases, nephrolithiasis/urolithiasis has been associated with renal insufficiency or acute renal failure. If signs or symptoms of nephrolithiasis/urolithiasis occur, (including flank pain, with or without hematuria or microscopic hematuria), temporary interruption (e.g., 1-3 days) or discontinuation of therapy may be considered. **Adequate**

hydration is recommended in all patients treated with CRIXIVAN. (See ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION, *Nephrolithiasis/Urolithiasis*.)

Hemolytic Anemia

Acute hemolytic anemia, including cases resulting in death, has been reported in patients treated with CRIXIVAN. Once a diagnosis is apparent, appropriate measures for the treatment of hemolytic anemia should be instituted, including discontinuation of CRIXIVAN.

Hepatitis

Hepatitis including cases resulting in hepatic failure and death has been reported in patients treated with CRIXIVAN. Because the majority of these patients had confounding medical conditions and/or were receiving concomitant therapy(ies), a causal relationship between CRIXIVAN and these events has not been established.

Hyperglycemia

New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus and hyperglycemia have been reported during post-marketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

Drug Interactions

Concomitant use of CRIXIVAN with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including CRIXIVAN, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin or cerivastatin). The risk of myopathy including rhabdomyolysis may be increased when HIV protease inhibitors, including CRIXIVAN, are used in combination with these drugs.

Concomitant use of CRIXIVAN and St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is not recommended. Coadministration of CRIXIVAN and St. John's wort has been shown to substantially decrease indinavir concentrations (see CLINICAL PHARMACOLOGY, *Pharmacokinetics, Drugs That Should Not Be Coadministered With CRIXIVAN*) and may lead to loss of virologic response and possible resistance to CRIXIVAN or to the class of protease inhibitors.

PRECAUTIONS

General

Indirect hyperbilirubinemia has occurred frequently during treatment with CRIXIVAN and has infrequently been associated with increases in serum transaminases (see also ADVERSE REACTIONS, *Clinical Trials* and *Post-Marketing Experience*). It is not known whether CRIXIVAN will exacerbate the physiologic hyperbilirubinemia seen in neonates. (See *Pregnancy*.)

Coexisting Conditions

Patients with hemophilia: There have been reports of spontaneous bleeding in patients with hemophilia A and B treated with protease inhibitors. In some patients, additional factor VIII was required. In many of the reported cases, treatment with protease inhibitors was continued or restarted. A causal relationship between protease inhibitor therapy and these episodes has not been established. (See ADVERSE REACTIONS, *Post-Marketing Experience*.)

Patients with hepatic insufficiency due to cirrhosis: In these patients, the dosage of CRIXIVAN should be lowered because of decreased metabolism of CRIXIVAN (see DOSAGE AND ADMINISTRATION).

Patients with renal insufficiency: Patients with renal insufficiency have not been studied.

Fat Redistribution

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving protease inhibitors. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Information for Patients

CRIXIVAN is not a cure for HIV infection and patients may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of CRIXIVAN are unknown at

this time. CRIXIVAN has not been shown to reduce the risk of transmission of HIV to others through sexual contact or blood contamination.

Patients should be advised to remain under the care of a physician when using CRIXIVAN and should not modify or discontinue treatment without first consulting the physician. Therefore, if a dose is missed, patients should take the next dose at the regularly scheduled time and should not double this dose. Therapy with CRIXIVAN should be initiated and maintained at the recommended dosage.

CRIXIVAN may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar (see CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption* and DOSAGE AND ADMINISTRATION). Ingestion of CRIXIVAN with a meal high in calories, fat, and protein reduces the absorption of indinavir.

Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving protease inhibitors and that the cause and long-term health effects of these conditions are not known at this time.

CRIXIVAN Capsules are sensitive to moisture. Patients should be informed that CRIXIVAN should be stored and used in the original container and the desiccant should remain in the bottle.

Drug Interactions

Delavirdine

Due to an increase in indinavir plasma concentrations (preliminary results), a dosage reduction of indinavir should be considered when CRIXIVAN and delavirdine are coadministered. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Delavirdine;* CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Delavirdine.*)

Efavirenz

Due to a decrease in the plasma concentrations of indinavir, a dosage increase of indinavir is recommended when CRIXIVAN and efavirenz are coadministered. No adjustment of the dose of efavirenz is necessary when given with indinavir. (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Efavirenz*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Efavirenz.*)

Itraconazole

Itraconazole is an inhibitor of P-450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN and itraconazole are coadministered (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Itraconazole*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Itraconazole*).

Ketoconazole

Ketoconazole is an inhibitor of P-450 3A4 that increases plasma concentrations of indinavir. Therefore, a dosage reduction of indinavir is recommended when CRIXIVAN and ketoconazole are coadministered (see DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Ketoconazole*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Ketoconazole*).

Rifabutin

When rifabutin and CRIXIVAN are coadministered, there is an increase in the plasma concentrations of rifabutin and a decrease in the plasma concentrations of indinavir. A dosage reduction of rifabutin and a dosage increase of CRIXIVAN are necessary when rifabutin is coadministered with CRIXIVAN. The suggested dose adjustments are expected to result in rifabutin concentrations at least 50% higher than typically observed when rifabutin is administered alone at its usual dose (300 mg/day) and indinavir concentrations which may be slightly less than typically observed when indinavir is administered alone at its usual dose (800 mg every 8 hours). (See DOSAGE AND ADMINISTRATION, *Concomitant Therapy, Rifabutin*; CLINICAL PHARMACOLOGY, *Drug Interactions, Drugs Requiring Dose Modification, Rifabutin*.)

Rifampin

Rifampin is a potent inducer of P-450 3A4 that markedly diminishes plasma concentrations of indinavir. Therefore, CRIXIVAN and rifampin should not be coadministered (see CLINICAL PHARMACOLOGY, *Drugs That Should Not Be Coadministered With CRIXIVAN*).

Other

If CRIXIVAN and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach; a normal (acidic) gastric pH may be necessary for optimum absorption of indinavir, whereas acid rapidly degrades didanosine which is formulated with buffering agents to increase pH (consult the manufacturer's product circular for didanosine).

Interactions between indinavir and less potent CYP3A4 inducers than rifampin, such as phenobarbital, phenytoin, carbamazepine, and dexamethasone have not been studied. These agents should be used with caution if administered concomitantly with indinavir because decreased indinavir plasma concentrations may result.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in mice and rats. In mice, no increased incidence of any tumor type was observed. The highest dose tested in rats was 640 mg/kg/day; at this dose a statistically significant increased incidence of thyroid adenomas was seen only in male rats. At that dose, daily systemic exposure in rats was approximately 1.3 times higher than daily systemic exposure in humans. No evidence of mutagenicity or genotoxicity was observed in *in vitro* microbial mutagenesis (Ames) tests, *in vitro* alkaline elution assays for DNA breakage, *in vitro* and *in vivo* chromosomal aberration studies, and *in vitro* mammalian cell mutagenesis assays. No treatment-related effects on mating, fertility, or embryo survival were seen in female rats and no treatment-related effects on mating performance were seen in male rats at doses providing systemic exposure comparable to or slightly higher than that with the clinical dose. In addition, no treatment-related effects were observed in fecundity or fertility of untreated females mated to treated males.

Pregnancy

Pregnancy Category C: Developmental toxicity studies were performed in rabbits (at doses up to 240 mg/kg/day), dogs (at doses up to 80 mg/kg/day), and rats (at doses up to 640 mg/kg/day). The highest doses in these studies produced systemic exposures in these species comparable to or slightly greater than human exposure. No treatment-related external, visceral, or skeletal changes were observed in rabbits or dogs. No treatment-related external or visceral changes were observed in rats. Treatment-related increases over controls in the incidence of supernumerary ribs (at exposures at or below those in humans) and of cervical ribs (at exposures comparable to or slightly greater than those in humans) were seen in rats. In all three species, no treatment-related effects on embryonic/fetal survival or fetal weights were observed.

In rabbits, at a maternal dose of 240 mg/kg/day, no drug was detected in fetal plasma 1 hour after dosing. Fetal plasma drug levels 2 hours after dosing were approximately 3% of maternal plasma drug levels. In dogs, at a maternal dose of 80 mg/kg/day, fetal plasma drug levels were approximately 50% of maternal plasma drug levels both 1 and 2 hours after dosing. In rats, at maternal doses of 40 and 640 mg/kg/day, fetal plasma drug levels were approximately 10 to 15% and 10 to 20% of maternal plasma drug levels 1 and 2 hours after dosing, respectively.

Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1 to 2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

Hyperbilirubinemia has occurred during treatment with CRIXIVAN (see PRECAUTIONS and ADVERSE REACTIONS). It is unknown whether CRIXIVAN administered to the mother in the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates.

There are no adequate and well-controlled studies in pregnant women. CRIXIVAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Antiviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to CRIXIVAN, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing Mothers

Studies in lactating rats have demonstrated that indinavir is excreted in milk. Although it is not known whether CRIXIVAN is excreted in human milk, there exists the potential for adverse effects from indinavir in nursing infants. Mothers should be instructed to discontinue nursing if they are receiving CRIXIVAN. This is consistent with the recommendation by the U.S. Public Health Service Centers for Disease Control and Prevention that HIV-infected mothers not breast-feed their infants to avoid risking postnatal transmission of HIV.

Pediatric Use

The optimal dosing regimen for use of indinavir in pediatric patients has not been established. A dose of 500 mg/m^2 every eight hours has been studied in uncontrolled studies of 70 children, 3 to 18 years of age. The pharmacokinetic profiles of indinavir at this dose were not comparable to profiles previously observed in adults receiving the recommended dose (see **CLINICAL PHARMACOLOGY**, *Pediatric*). Although viral suppression was observed in some of the 32 children who were followed on this regimen through 24 weeks, a substantially higher rate of nephrolithiasis was reported when compared to adult historical data (see **WARNINGS**, *Nephrolithiasis/Urolithiasis*). Physicians considering the use of indinavir in pediatric patients without other protease inhibitor options should be aware of the limited data available in this population and the increased risk of nephrolithiasis.

ADVERSE REACTIONS

Clinical Trials in Adults

Nephrolithiasis/urolithiasis, including flank pain with or without hematuria (including microscopic hematuria), has been reported in approximately 9.3% (193/2071) of patients receiving CRIXIVAN in clinical trials at the recommended dose, compared to 1.8% in the control arms. Of the patients treated with CRIXIVAN who developed nephrolithiasis/urolithiasis, 3.1% (6/193) were reported to develop hydronephrosis and 3.1% (6/193) underwent stent placement. Following the acute episode, 3.6% (7/193) of patients discontinued therapy. (See WARNINGS and DOSAGE AND ADMINISTRATION, Nephrolithiasis/Urolithiasis.)

Asymptomatic hyperbilirubinemia (total bilirubin ≥2.5 mg/dL), reported predominantly as elevated indirect bilirubin, has occurred in approximately 14% of patients treated with CRIXIVAN. In <1% this was associated with elevations in ALT or AST.

Hyperbilirubinemia and nephrolithiasis/urolithiasis occurred more frequently at doses exceeding 2.4 g/day compared to doses ≤2.4 g/day.

Clinical adverse experiences reported in ≥2% of patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 5.

Table 5
Clinical Adverse Experiences Reported in ≥2% of Patients

	Study 028 Considered Drug-Related and of Moderate or Severe Intensity			Study ACTG 320 of Unknown Drug Relationship and of Severe or Life-threatening Intensity	
Adverse Experience	CRIXIVAN Percent (n=332)	CRIXIVAN plus Zidovudine Percent (n=332)	Zidovudine Percent (n=332)	CRIXIVAN plus Zidovudine plus Lamivudine Percent (n=571)	Zidovudine plus Lamivudine Percent (n=575)
Body as a Whole					
Abdominal pain	16.6	16.0	12.0	1.9	0.7
Asthenia/fatigue	2.1	4.2	3.6	2.4	4.5
Fever	1.5	1.5	2.1	3.8	3.0
Malaise	2.1	2.7	1.8	0	0
Digestive System					
Nausea	11.7	31.9	19.6	2.8	1.4
Diarrhea	3.3	3.0	2.4	0.9	1.2
Vomiting	8.4	17.8	9.0	1.4	1.4
Acid regurgitation	2.7	5.4	1.8	0.4	0
Anorexia	2.7	5.4	3.0	0.5	0.2
Appetite increase	2.1	1.5	1.2	0	0
Dyspepsia	1.5	2.7	0.9	0	0
Jaundice	1.5	2.1	0.3	0	0
Hemic and Lymphatic System					
Anemia	0.6	1.2	2.1	2.4	3.5
Musculoskeletal System					
Back pain	8.4	4.5	1.5	0.9	0.7
Nervous System/Psychiatric					
Headache	5.4	9.6	6.0	2.4	2.8
Dizziness	3.0	3.9	0.9	0.5	0.7
Somnolence	2.4	3.3	3.3	0	0
Skin and Skin Appendage					
Pruritus	4.2	2.4	1.8	0.5	0
Rash	1.2	0.6	2.4	1.1	0.5
Respiratory System					
Cough	1.5	0.3	0.6	1.6	1.0
Difficulty breathing/ dyspnea/shortness of breath	0	0.6	0.3	1.8	1.0
Urogenital System					
Nephrolithiasis/urolithiasis*	8.7	7.8	2.1	2.6	0.3
Dysuria	1.5	2.4	0.3	0.4	0.2
Special Senses					
Taste perversion	2.7	8.4	1.2	0.2	0

* Including renal colic, and flank pain with and without hematuria

In Phase I and II controlled trials, the following adverse events were reported significantly more frequently by those randomized to the arms containing CRIXIVAN than by those randomized to nucleoside analogues: rash, upper respiratory infection, dry skin, pharyngitis, taste perversion.

Selected laboratory abnormalities of severe or life-threatening intensity reported in patients treated with CRIXIVAN alone, CRIXIVAN in combination with zidovudine or zidovudine plus lamivudine, zidovudine alone, or zidovudine plus lamivudine are presented in Table 6.

Table 6
Selected Laboratory Abnormalities of Severe or Life-threatening Intensity
Reported in Studies 028 and ACTG 320

	Study 028			Study ACTG 320	
	CRIXIVAN	CRIXIVAN plus Zidovudine	Zidovudine	CRIXIVAN plus Zidovudine plus Lamivudine	Zidovudine plus Lamivudine
	Percent (n=329)	Percent (n=320)	Percent (n=330)	Percent (n=571)	Percent (n=575)
Hematology					
Decreased hemoglobin <7.0 g/dL	0.6	0.9	3.3	2.4	3.5
Decreased platelet count <50 THS/mm^3	0.9	0.9	1.8	0.2	0.9
Decreased neutrophils <0.75 THS/mm^3	2.4	2.2	6.7	5.1	14.6
Blood chemistry					
Increased ALT >500% ULN*	4.9	4.1	3.0	2.6	2.6
Increased AST >500% ULN	3.7	2.8	2.7	3.3	2.8
Total serum bilirubin >250% ULN	11.9	9.7	0.6	6.1	1.4
Increased serum amylase >200% ULN	2.1	1.9	1.8	0.9	0.3
Increased glucose >250 mg/dL	0.9	0.9	0.6	1.6	1.9
Increased creatinine >300% ULN	0	0	0.6	0.2	0

* Upper limit of the normal range.

Post-Marketing Experience

Body As A Whole: redistribution/accumulation of body fat (see PRECAUTIONS, *Fat Redistribution*).

Cardiovascular System: cardiovascular disorders including myocardial infarction and angina pectoris.

Digestive System: liver function abnormalities; hepatitis including reports of hepatic failure (see WARNINGS); pancreatitis; jaundice; abdominal distention; dyspepsia.

Hematologic: increased spontaneous bleeding in patients with hemophilia (see PRECAUTIONS); acute hemolytic anemia (see WARNINGS).

Endocrine/Metabolic: new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia (see WARNINGS).

Hypersensitivity: anaphylactoid reactions; urticaria.

Musculoskeletal System: arthralgia.

Nervous System/Psychiatric: oral paresthesia; depression.

Skin and Skin Appendage: rash including erythema multiforme and Stevens-Johnson Syndrome; hyperpigmentation; alopecia; ingrown toenails and/or paronychia; pruritus.

Urogenital System: nephrolithiasis/urolithiasis; in some cases resulting in renal insufficiency or acute renal failure (see WARNINGS); interstitial nephritis sometimes with indinavir crystal deposits; in some patients, the interstitial nephritis did not resolve following discontinuation of CRIXIVAN; crystalluria; dysuria.

Laboratory Abnormalities

Increased serum triglycerides; increased serum cholesterol.

OVERDOSAGE

There have been more than 60 reports of acute or chronic human overdosage (up to 23 times the recommended total daily dose of 2400 mg) with CRIXIVAN. The most commonly reported symptoms were renal (e.g., nephrolithiasis/urolithiasis, flank pain, hematuria) and gastrointestinal (e.g., nausea, vomiting, diarrhea).

It is not known whether CRIXIVAN is dialyzable by peritoneal or hemodialysis.

DOSAGE AND ADMINISTRATION

The recommended dosage of CRIXIVAN is 800 mg (usually **two** 400-mg capsules) orally every 8 hours.

CRIXIVAN must be taken at intervals of 8 hours. For optimal absorption, CRIXIVAN should be administered without food but with water 1 hour before or 2 hours after a meal. Alternatively, CRIXIVAN may be administered with other liquids such as skim milk, juice, coffee, or tea, or with a light meal, e.g., dry toast with jelly, juice, and coffee with skim milk and sugar; or corn flakes, skim milk and sugar. (See CLINICAL PHARMACOLOGY, *Effect of Food on Oral Absorption*.)

To ensure adequate hydration, it is recommended that adults drink at least 1.5 liters (approximately 48 ounces) of liquids during the course of 24 hours.

Concomitant Therapy (See CLINICAL PHARMACOLOGY, *Drug Interactions*, and/or PRECAUTIONS, *Drug Interactions*.)

Delavirdine

Dose reduction of CRIXIVAN to 600 mg every 8 hours should be considered when administering delavirdine 400 mg three times a day.

Didanosine

If indinavir and didanosine are administered concomitantly, they should be administered at least one hour apart on an empty stomach (consult the manufacturer's product circular for didanosine).

Efavirenz

Dose increase of CRIXIVAN to 1000 mg every 8 hours is recommended when administering efavirenz concurrently (consult the manufacturer's product circular for efavirenz).

Itraconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering itraconazole 200 mg twice daily concurrently.

Ketoconazole

Dose reduction of CRIXIVAN to 600 mg every 8 hours is recommended when administering ketoconazole concurrently.

Rifabutin

Dose reduction of rifabutin to half the standard dose (consult the manufacturer's product circular for rifabutin) and a dose increase of CRIXIVAN to 1000 mg (**three** 333-mg capsules) every 8 hours are recommended when rifabutin and CRIXIVAN are coadministered.

Hepatic Insufficiency

The dosage of CRIXIVAN should be reduced to 600 mg every 8 hours in patients with mild-to-moderate hepatic insufficiency due to cirrhosis.

Nephrolithiasis/Urolithiasis

In addition to adequate hydration, medical management in patients who experience nephrolithiasis/urolithiasis may include temporary interruption (e.g., 1 to 3 days) or discontinuation of therapy.

HOW SUPPLIED

CRIXIVAN Capsules are supplied as follows:

No. 3755 — 100 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 100 mg"** in green and a radial green band on the body. Available as:

NDC 0006-0570-62 unit of use bottles of 180 (with desiccant).

No. 3756 — 200 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 200 mg"** in blue. Available as:

NDC 0006-0571-42 unit-of-use bottles of 270 (with desiccant)

NDC 0006-0571-43 unit-of-use bottles of 360 (with desiccant).

No. 3802 — 333 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 333 mg"** in red and a radial red band on the body. Available as:

NDC 0006-0574-65 unit-of-use bottles of 135 (with desiccant).

No. 3758 — 400 mg capsules: semi-translucent white capsules coded **"CRIXIVAN™ 400 mg"** in green. Available as:

NDC 0006-0573-42 unit-dose packages of 42

NDC 0006-0573-62 unit-of-use bottles of 180 (with desiccant)
NDC 0006-0573-54 unit-of-use bottles of 90 (with desiccant)
NDC 0006-0573-18 unit-of-use bottles of 18 (with desiccant).

Storage

Bottles: Store in a tightly-closed container at room temperature, 15-30°C (59-86°F). Protect from moisture.

CRIXIVAN Capsules are sensitive to moisture. CRIXIVAN should be dispensed and stored in the original container. The desiccant should remain in the original bottle.

Unit-Dose Packages: Store at room temperature, 15-30°C (59-86°F). Protect from moisture.

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CRIXIVAN®* (indinavir sulfate) Capsules

Patient Information about

CRIXIVAN (KRIK-sih-van)

for HIV (Human Immunodeficiency Virus) Infection

Generic name: indinavir (in-DIH-nuh-veer) sulfate

Please read this information before you start taking CRIXIVAN. Also, read the leaflet each time you renew your prescription, just in case anything has changed. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss CRIXIVAN when you start taking your medication and at regular checkups. You should remain under a doctor's care when using CRIXIVAN and should not change or stop treatment without first talking with your doctor.

What is CRIXIVAN?

CRIXIVAN is an oral capsule used for the treatment of HIV (Human Immunodeficiency Virus). HIV is the virus that causes AIDS (acquired immune deficiency syndrome). CRIXIVAN is a type of HIV drug called a protease (PRO-tee-ase) inhibitor.

How does CRIXIVAN work?

CRIXIVAN is a protease inhibitor that fights HIV. CRIXIVAN can help reduce your chances of getting illnesses associated with HIV. CRIXIVAN can also help lower the amount of HIV in your body (called "viral load") and raise your CD4 (T) cell count. CRIXIVAN may not have these effects in all patients.

CRIXIVAN is usually prescribed with other anti-HIV drugs such as ZDV (also called AZT), 3TC, ddI, ddC, or d4T. CRIXIVAN works differently from these other anti-HIV drugs. Talk with your doctor about how you should take CRIXIVAN.

How should I take CRIXIVAN?

There are six important things you must do to help you benefit from CRIXIVAN:

1. **Take CRIXIVAN capsules every day as prescribed by your doctor.** Continue taking CRIXIVAN unless your doctor tells you to stop. Take the exact amount of CRIXIVAN that your doctor tells you to take, right from the very start. To help make sure you will benefit from CRIXIVAN, you must not skip doses or take "drug holidays". If you don't take CRIXIVAN as prescribed, the activity of CRIXIVAN may be reduced (due to resistance).

2. **Take CRIXIVAN capsules every 8 hours around the clock, *every day*.** It may be easier to remember to take CRIXIVAN if you take it at the same time every day. If you have questions about when to take CRIXIVAN, your doctor or health care provider can help you decide what schedule works for you.

3. **If you miss a dose by more than 2 hours, wait and then take the next dose at the regularly scheduled time.** However, if you miss a dose by less than 2 hours, take your missed dose immediately. Then take your next dose at the regularly scheduled time. Do not take more or less than your prescribed dose of CRIXIVAN at any one time.

4. **Take CRIXIVAN with water.** You can also take CRIXIVAN with other beverages such as skim or non-fat milk, juice, coffee, or tea.

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5. **Ideally, take each dose of CRIXIVAN without food but with water at least one hour before or two hours after a meal.** Or you can take CRIXIVAN with a light meal. Examples of light meals include:
   dry toast with jelly, juice, and coffee (with skim or non-fat milk and sugar if you want)
   cornflakes with skim or non-fat milk and sugar
   Do not take CRIXIVAN at the same time as any meals that are high in calories, fat, and protein (for example — a bacon and egg breakfast). When taken at the same time as CRIXIVAN, these foods can interfere with CRIXIVAN being absorbed into your bloodstream and may lessen its effect.

6. **It is critical to drink plenty of fluids while taking CRIXIVAN.** Adults should drink at least six 8-ounce glasses of liquids (preferably water) throughout the day, every day. Your health care provider will give you further instructions on the amount of fluid that you should drink. **CRIXIVAN can cause kidney stones.** Having enough fluids in your body should help reduce the chances of forming a kidney stone. Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Does CRIXIVAN cure HIV or AIDS?

CRIXIVAN is not a cure for HIV or AIDS. People taking CRIXIVAN may still develop infections or other conditions associated with HIV. Because of this, it is very important for you to remain under the care of a doctor. Although CRIXIVAN is not a cure for HIV or AIDS, CRIXIVAN can help reduce your chances of getting illnesses, including death, associated with HIV. CRIXIVAN may not have these effects in all patients.

Does CRIXIVAN reduce the risk of passing HIV to others?

CRIXIVAN has not been shown to reduce the risk of passing HIV to others through sexual contact or blood contamination.

Who should not take CRIXIVAN?

Do not take CRIXIVAN if you have had a serious allergic reaction to CRIXIVAN or any of its components.

What other medical problems or conditions should I discuss with my doctor?

Talk to your doctor if:
- You are pregnant or if you become pregnant while you are taking CRIXIVAN.
  We do not yet know how CRIXIVAN affects pregnant women or their developing babies.
- You are breast-feeding. You should stop breast-feeding if you are taking CRIXIVAN.

Also talk to your doctor if you have:
- Problems with your liver, especially if you have mild or moderate liver disease caused by cirrhosis.
- Problems with your kidneys.
- Diabetes
- Hemophilia
- High cholesterol and you are taking cholesterol-lowering medicines called “statins”.

Tell your doctor about any medicines you are taking or plan to take, including non-prescription medicines, herbal products including St. John’s wort (*Hypericum perforatum*), or dietary supplements.

Can CRIXIVAN be taken with other medications?**

Drugs you should not take with CRIXIVAN:

SELDANE®
(terfenadine)
VERSED®
(midazolam)
ORAP®
(pimozide)
PROPULSID®
(cisapride)

HISMANAL®
(astemizole)
HALCION®
(triazolam)
Ergot medications
(e.g., Wigraine® and Cafergot®)

Taking CRIXIVAN with the above medications could result in serious or life-threatening problems (such as irregular heartbeat or excessive sleepiness).

In addition, you should not take CRIXIVAN with the following:

Rifampin, known as RIFADIN®, RIFAMATE®, RIFATER®, or RIMACTANE®.

It is not recommended to take CRIXIVAN with the cholesterol-lowering drugs MEVACOR* (lovastatin) or ZOCOR* (simvastatin) because of possible drug interactions. There is also an increased risk of drug interactions between CRIXIVAN and LIPITOR® (atorvastatin) and BAYCOL® (cerivastatin); talk to your doctor before you take any of these cholesterol-reducing drugs with CRIXIVAN.

Taking CRIXIVAN with St. John's wort (*Hypericum perforatum*), an herbal product sold as a dietary supplement, or products containing St. John's wort is not recommended. Taking St. John's wort has been shown to decrease CRIXIVAN levels and may lead to increased viral load and possible resistance to CRIXIVAN or cross resistance to other antiretroviral drugs.

Drugs you can take with CRIXIVAN include:

RETROVIR®
(zidovudine, ZDV
also called AZT)

EPIVIR™
(lamivudine, 3TC)

ZERIT®
(stavudine, d4T)

isoniazid
(INH)

BACTRIM®/SEPTRA®
(trimethoprim/sulfamethoxazole)

DIFLUCAN®
(fluconazole)

BIAXIN®
(clarithromycin)

ORTHO-NOVUM 1/35®
(oral contraceptive)

TAGAMET®
(cimetidine)

Methadone

VIDEX® (didanosine, ddI) — If you take CRIXIVAN with VIDEX, take them at least one hour apart.

MYCOBUTIN® (rifabutin) — If you take CRIXIVAN with MYCOBUTIN, your doctor may adjust both the dose of MYCOBUTIN and the dose of CRIXIVAN.

NIZORAL® (ketoconazole) — If you take CRIXIVAN with NIZORAL, your doctor may adjust the dose of CRIXIVAN.

RESCRIPTOR® (delavirdine) — If you take CRIXIVAN with RESCRIPTOR, your doctor may adjust the dose of CRIXIVAN.

SPORANOX® (itraconazole) — If you take CRIXIVAN with SPORANOX, your doctor may adjust the dose of CRIXIVAN.

SUSTIVA™ (efavirenz) — If you take CRIXIVAN with SUSTIVA, your doctor may adjust the dose of CRIXIVAN.

Talk to your doctor about any medications you are taking.

What are the possible side effects of CRIXIVAN?

Like all prescription drugs, CRIXIVAN can cause side effects. The following is **not** a complete list of side effects reported with CRIXIVAN when taken either alone or with other anti-HIV drugs. Do not rely on this leaflet alone for information about side effects. Your doctor can discuss with you a more complete list of side effects.

Some patients treated with CRIXIVAN developed kidney stones. In some of these patients this led to more severe kidney problems, including kidney failure or inflammation of the kidneys. Drinking at least six 8-ounce glasses of liquids (preferably water) each day should help reduce the chances of forming a kidney stone (see **How should I take CRIXIVAN?).** Call your doctor or other health care provider if you develop kidney pains (middle to lower stomach or back pain) or blood in the urine.

Some patients treated with CRIXIVAN have had rapid breakdown of red blood cells (hemolytic anemia) which in some cases was severe or resulted in death.

Some patients treated with CRIXIVAN have had liver problems including liver failure and death. Some patients had other illnesses or were taking other drugs. It is uncertain if CRIXIVAN caused these liver problems.

Diabetes and high blood sugar (hyperglycemia) have occurred in patients taking protease inhibitors. In some of these patients, this led to ketoacidosis, a serious condition caused by poorly controlled blood sugar. Some patients had diabetes before starting protease inhibitors, others did not. Some patients required adjustments to their diabetes medication. Others needed new diabetes medication.

In some patients with hemophilia, increased bleeding has been reported.

Severe muscle pain and weakness have occurred in patients taking protease inhibitors, including CRIXIVAN, together with some of the cholesterol-lowering medicines called “statins”. Call your doctor if you develop severe muscle pain or weakness.

Changes in body fat have been seen in some patients taking protease inhibitors. These changes may include increased amount of fat in the upper back and neck (“buffalo hump”), breast, and around the trunk. Loss of fat from the legs and arms may also happen. The cause and long term health effects of these conditions are not known at this time.

Clinical Studies

Increases in bilirubin (one laboratory test of liver function) have been reported in approximately 10% of patients. Usually, this finding has not been associated with liver problems. However, on rare occasions, a person may develop yellowing of the skin and/or eyes.

Side effects occurring in 2% or more of patients included: abdominal pain, fatigue or weakness, low red blood cell count, flank pain, painful urination, feeling unwell, nausea, upset stomach, diarrhea, vomiting, acid regurgitation, increased or decreased appetite, back pain, headache, dizziness, taste changes, rash, itchy skin, yellowing of the skin and/or eyes, upper respiratory infection, dry skin, and sore throat.

Swollen kidneys due to blocked urine flow occurred rarely.

Marketing Experience

Other side effects reported since CRIXIVAN has been marketed include: allergic reactions; severe skin reactions; yellowing of the skin and/or eyes; heart problems including heart attack; abdominal swelling; indigestion; inflammation of the kidneys; inflammation of the pancreas; joint pain; depression; itching; hives; change in skin color; hair loss; ingrown toenails with or without infection; crystals in the urine; painful urination; and numbness of the mouth.

Tell your doctor promptly about these or any other unusual symptoms. If the condition persists or worsens, seek medical attention.

How should I store CRIXIVAN capsules?

- Keep CRIXIVAN capsules in the bottle they came in and at room temperature (59°-86°F).
- Keep CRIXIVAN capsules dry by leaving the small desiccant "pillow" in the bottle. Keep the bottle closed.

This medication was prescribed for your particular condition. Do not use it for any other condition or give it to anybody else. Keep CRIXIVAN and all medicines out of the reach of children. If you suspect that more than the prescribed dose of this medicine has been taken, contact your local poison control center or emergency room immediately.

This leaflet provides a summary of information about CRIXIVAN. If you have any questions or concerns about either CRIXIVAN or HIV, talk to your doctor.

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